Wilson Disease – an Overview

Disease Summary

Wilson disease is an autosomal recessive disorder of copper metabolism characterized by abnormal accumulation of copper in the liver, brain, and other organs.\(^1\) Prevalence of the disease is approximately 1 in 30,000 persons worldwide, and 1 in 10,000 in China, Japan, and Sardinia.\(^1,2\) Wilson disease typically first presents between the ages of 6 and 50 years, with acute or chronic liver disease (40% of affected), neurological movement disorders (40% of affected), or psychiatric disturbances such as depression or neurotic behaviors (20% of affected).\(^1\) While all three types of manifestations can be present, this is rarely the case.\(^1\) In children, liver disease is the most common presenting manifestation.\(^1\) Early diagnosis of Wilson disease is very important as early treatment can preserve liver function and prevent the development of neuropsychiatric illness.\(^1\)

Wilson disease has been linked to mutations in the gene ATP7B, which codes for a P-type copper-transporting ATPase.\(^2\) Presentation of the disease is highly variable even among families with the same causative mutations in ATP7B.\(^2,3\) Mutations that cause complete lack of function (e.g., nonsense and other mutations that cause truncation of the encoded protein) have been associated with earlier onset of the disease and, potentially, a more severe phenotype than mutations that allow residual activity (e.g., missense mutations that cause subtle changes in the encoded protein).\(^1\) However, in general, severity or presentation of Wilson disease is difficult to predict from the mutation due to the influence of environmental and other genetic factors.\(^3\) Among common mutations, H1069Q is found in 35% to 45% of disease alleles in European population and R778L is found in about 57% of disease alleles in Asians under the age of 18.\(^1\)

Wilson disease is usually diagnosed based on clinical symptoms and evidence of low serum ceruloplasmin and high urinary copper from biochemical testing.\(^1\) An important clinical finding is the presence of Kayser-Fleischer rings in the cornea, which is observed in 50-60% of individuals with liver disease and 90% of individuals with either neurologic findings or psychiatric disturbance.\(^1\) Biochemical testing has limitations in that age-specific reference ranges are required for appropriate interpretation of results (especially in young children), collection of urine over three days may be difficult, and the carrier (heterozygote) state and the presymptomatic state cannot be reliably distinguished.\(^1,4\) Genetic testing can confirm the diagnosis of Wilson disease and resolve equivocal biochemical test results.\(^5\) Once the mutations causing Wilson disease in a specific family have been identified, genetic testing for these mutations can also identify presymptomatic individuals among the patient’s relatives, allowing preventative treatment. By distinguishing presymptomatic family members from heterozygous carriers, genetic testing can help to protect heterozygous carriers from unnecessary treatment.

For additional information, see Tables 1-2 below and references 1-5.
Table 1: Disease Facts about WD  (based on references 1-7, unless otherwise noted)

<table>
<thead>
<tr>
<th>Disease Fact</th>
<th>Wilson Disease</th>
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<tbody>
<tr>
<td>MIM* number</td>
<td>277900</td>
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<tr>
<td>Estimated Prevalence</td>
<td>1:30,000 (1)</td>
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<tr>
<td>Average Age at Diagnosis</td>
<td>Childhood or adolescence (liver disease) Young adults (neuropsychiatric illness)</td>
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| Typical Symptoms | Hepatic: Liver disease, including recurrent jaundice, acute or chronic hepatitis, fulminant hepatic failure, and hemolytic anemia  
Neurological: movement disorders, drooling  
Psychiatric: depression, neuroses, personality changes  
Ophthalmological: Kayser-Fleischer rings in cornea |
| Therapy | Copper chelation treatment (penicillamine, trientine, tetrahiomolybdate)  
Copper absorption blocking treatment (zinc acetate)  
Restriction of high-copper foods (shellfish, liver, chocolate, mushrooms, nuts)  
Orthotopic liver transplantation when other treatments fail or cannot be tolerated |

*MIM: Mendelian Inheritance in Man, see http://www.ncbi.nlm.nih.gov/omim

Table 2: Molecular Genetics of WD  (based on references 1-7, unless otherwise noted)

<table>
<thead>
<tr>
<th>Gene (Protein)</th>
<th>Transmission</th>
<th>Mutation type</th>
<th>Penetration</th>
<th>Comments</th>
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<tr>
<td>ATP7B (P-type ATPase)</td>
<td>Autosomal recessive</td>
<td>Loss-of-function</td>
<td>Unknown</td>
<td>Mutations causing complete lack of function are associated with early onset of disease, while other specific mutations are associated with milder severity and later onset of disease.</td>
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References